UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/597,008	07/06/2006	Robert Dean Dally	X-16846M	4664

25885 7590 08/28/2009

ELI LILLY & COMPANY
PATENT DIVISION
P.O. BOX 6288
INDIANAPOLIS, IN 46206-6288

EXAMINER	
CHANG, CELIA C	

ART UNIT	PAPER NUMBER
1625	

NOTIFICATION DATE	DELIVERY MODE
08/28/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patents@lilly.com

Office Action Summary	Application No.	Applicant(s)	
	10/597,008	DALLY ET AL.	
	Examiner	Art Unit	
	Celia Chang	1625	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 May 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,6,9,11,14,16,19,20,23,36,37,41,43,45,48,50,52,53,58 and 60* is/are pending in the application.

4a) Of the above claim(s) *37, 41, 43* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *1,2,6,9,11,14,16,19,20,23,36,45,48,50,52,53,58 and 60* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's election of Group I, claims 48, 50, and 45 in part when m=1, R-X^1 forms a ring, i.e. tetracyclic ring compounds in the reply filed on May 18, 2009 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 48, 50 and claims 1-2, 6, 9, 11, 14, 16, 19-20, 23, 36, 45, 52-53, 58 and 60 reading on m=l, R-$X^1$is tetracyclic ring are prosecuted. Claims 37, 41, 43 and the remaining subject matter of claims 1-2, 6, 9, 11, 14, 16, 19-20, 23, 36, 45, 52-53, 58 and 60 are withdrawn from consideration per 37 CFR 1.142(b).

2. Claims 1-2, 6, 9, 11, 14, 16, 19-20, 23, 36, 45, 48, 50, 52-53, 58 and 60 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claims contain subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The standard for determining whether the specification meets the enablement requirement was cast in the Supreme Court decision of *Mineral Separation v. Hyde*, 242 U.S. 261, 270 (1916), where the Supreme Court looked to whether the experimentation needed to practice an invention was undue or unreasonable. *Id.* An invention must be described so that any person skilled in the art can make and use the invention without undue experimentation. *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988). As stated in the MPEP 2164.01(a) "There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue". The analysis must consider all the evidence related to each of these factors, and any conclusion of nonenablement must be based on the evidence as a whole. *Id.* at 740, *Id.* at 1407. The factors to be considered herein are those set forth as the In re Wands, 8 USPQ 2nd 1400 (1988) decision.

The analysis is applied to the instant case.

Nature of invention and breadth of the claims

The claims are drawn to enormous number of compounds being useful in treating patho-physiological disorders through modulation of the estrogen receptor systems.

The state of the art, level of ordinary skill and predictability

Unlike mechanical or electrical art, the biological science using compounds in manipulating patho-physiological events is highly unpredictable. In the instant field, studies conducted using the analogous lead compound raloxifene has indicated that the instant tetracyclic ring system are analogous core as raloxifene (see Grese et al. J.. Med. Chem.. v.41, p. 1272-1283, particularly raloxifene p.1271 right column vs p.1274, tetrycyclic compound 4, right column and Wallace et al. p.843 right column). The substitution on the core system, particularly the 6- and 4'-hydroxyl moieties have studied extensively. It is well recognized in the art that:

> "*In particular, the 6-hydroxy and, to a lesser extent, the 4'-hydroxy substituents are important for receptor binding and in vitro activity and appear to mimic the corresponding 3- and 17β-hydroxy substituents of estradiol. Modified or additional substitution of the benzothiophene[core] generally results in reduced biological activity; however, some variance in the substitution pattern of the 2-aryl ring is tolerated. Indeed, the entire 2-aryl ring can be replaced by alkyl, cycloalkyl, or naphthyl substituents without disrupting the SERM profile of in vitro and in vivo biological activity, although increased steric bulk at the 4'-position leads to increased uterine stimulation. Several novel structural variants including 2-cyc]ohexyl, 2-naphthyl, and 6-carbomethoxy analogs maintain activity similar to that of raloxifene. Nevertheless, the 6-hydroxy-2-(4'-hydroxyphenyl) substitution pattern of raloxifene appears to be nearly optimal for both in vitro and in vivo activity, especially with respect to serum cholesterol reduction and protection against ovariectomy-induced bone loss without significant stimulation of the uterus." (see* Grese et al. recited on 1449, *p.*183, right column).

Particularly, consistent lower activity was observed for the instantly claimed substitution system being i.e. $CR^3R^{3a}OH$ or $CONR^8R^9$, $CO\text{-}OR^{10}$, see table 1, compound 10k (decrease IC50), table 2 compound 23c, 23d.

Working examples and amount of experimentation/guidance

The specification provided testing procedure without any results of any of the exemplified compounds having what activity. The estrogen receptor modulation is a very complex physiological system. There is no evidence that activity of one compound without testing data can predict activity of another compound. Especially, the point of novelty of the instantly claimed compounds have been evidenced in the art to be undesirable modification on the core system. Absent of efficacy information on "*in vitro* and *in vivo* activity, especially with respect to serum cholesterol reduction and protection against ovariectomy-induced bone loss without significant stimulation of the uterus" as described being necessary by the prior art (see

Grese recited on 1449, p.183 right column), the specification provided insufficient enablement for the claims.

3. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Celia Chang, Ph. D. whose telephone number is 571-272-0679. The examiner can normally be reached on Monday through Thursday from 8:30 am to 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet L. Andres, Ph. D., can be reached on 571-272-0867. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

OACS/Chang
Aug. 19, 2009

/Celia Chang/
Primary Examiner
Art Unit 1625